TREATMENT FOR DIABETES IN PATIENTS INAPPROPRIATE FOR METFORMIN THERAPY

The present invention relates to certain DPP-4 inhibitors for treating and/or preventing metabolic diseases, particularly diabetes (especially type 2 diabetes mellitus) and conditions related thereto, in patients for whom normal metformin therapy is not appropriate (due to intolerability or contraindication against metformin), as well as to the use of these DPP-4 inhibitors in said treatment and/or prevention. Pharmaceutical compositions and combinations for treating and/or preventing metabolic diseases (particularly diabetes) in these patients comprising a DPP-4 inhibitor as defined herein optionally together with one or more other active substances are also contemplated.

Type 2 diabetes mellitus is a common disease of increasing prevalence worldwide and may be associated with macrovascular complications such as cardiovascular disease, and/or microvascular complications such as blindness, neuropathy and/or renal impairment or failure.

There are various reasons why renal impairment can occur in people with diabetes. One of the typical long-term complications of diabetes is diabetic nephropathy, which can progress to renal failure in some cases.

Although intensive treatment of hyperglycemia can reduce the incidence of chronic damages, many patients with type 2 diabetes remain inadequately treated, partly because of limitations in long term efficacy, tolerability and dosing inconvenience of existing antihyperglycemic therapies.

Diet therapy and exercise therapy are essential in the treatment of diabetes mellitus. When these therapies do not sufficiently control the conditions of patients (especially their blood sugar level), an oral or non-oral antidiabetic agent is additionally used for the treatment of diabetes. Conventional antidiabetic or antihyperglycemic agents include, without being limited to, metformin, sulphonylureas, thiazolidinediones, glinides, alpha-glucosidase blockers, GLP-1 and GLP-1 analogues, as well as insulin and insulin analogues. However, the use of these conventional antidiabetic or antihyperglycemic agents can be associated with various adverse effects. For example, metformin can be associated with lactic acidosis or gastrointestinal side effects; sulfonylureas, glinides and insulin or insulin analogues can be associated with hypoglycemia or weight gain; thiazolidinediones can be associated with edema, bone fracture, weight gain or heart failure/cardiac effects; and alpha-glucosidase blockers and GLP-1 or GLP-1 analogues can be associated with gastrointestinal adverse effects (e.g. dyspepsia, flatulence or diarrhea, or nausea or vomiting).

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus. Metformin can be used alone or combined with other antihyperglycemic medications to improve glycemic control in metformin responsive type 2 diabetes patients. Metformin can also be of value in the treatment of obese or overweight diabetic patients or in patients with polycystic ovary syndrome. However, treatment with metformin can be associated with adverse symptoms, such as e.g. gastrointestinal symptoms or, occasionally, as a severe adverse effect, lactic acidosis (which can be fatal), for which one putative risk factor is decreased renal function. Further, since metformin is largely eliminated unchanged by the kidneys via glomerular filtration and tubular secretion, it is contraindicated in patients with renal disease or renal impairment. Thus, conventional metformin therapy can be inappropriate for certain patients, e.g. due to intolerability or contraindication against metformin.

The number of patients who are thus ineligible for metformin can be quite large and may include a considerable percentage of those who might otherwise benefit from the medication. Therefore, it remains a need in the art to provide efficacious, safe and tolerable antidiabetic therapies for these diabetic patients ineligible for metformin therapy.

In the monitoring of the treatment of diabetes mellitus the HbA1c value, the product of a non-enzymatic glycation of the haemoglobin B chain, is of exceptional importance. As its formation depends essentially on the blood sugar level and the life time of the erythrocytes the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar level of the preceding 4-12 weeks. Diabetic patients whose HbA1c level has been well controlled over a long time by more intensive diabetes treatment (i.e. <6.5% of the total haemoglobin in the sample) are significantly better protected from diabetic microangiopathy. The available treatments for diabetes can give the diabetic an average improvement in their HbA1c level of the order of 1.0-1.5%. This reduction in the HbA1C level is not sufficient in all diabetics to bring them into the desired target range of <7.0%, preferably <6.5% and more preferably <6% HbA1c.

Within glycemic control, in addition to improvement of the HbA1c level, other recommended therapeutic goals for type 2 diabetes mellitus patients are improvement of fasting plasma glucose (FPG) and of postprandial plasma glucose (PPG) levels to normal or as near normal as possible. Recommended desired target ranges of preprandial (fasting) plasma glucose are 90-130 mg/dL or <110 mg/dL, and of two-hour postprandial plasma glucose are <180 mg/dL or <140 mg/dL.

Within the meaning of this invention, inadequate or insufficient glycemic control means in particular a condition wherein patients show HbA1c values above 6.5%, in particular above 7.0%, even more preferably above 7.5%, especially above 8%. An embodiment of patients with inadequate or insufficient glycemic control include, without being limited to, patients having a HbA1c value from 7.5 to 10% (or, in another embodiment, from 7.5 to 11%). A special sub-embodiment of inadequately controlled patients refers to patients with poor glycemic control including, without being limited, patients having a HbA1c value≥9%.

Patients ineligible for metformin therapy within the meaning of the present invention include

- patients for whom metformin therapy is contraindicated, e.g. patients having one or more contraindications against metformin therapy according to label, such as for example patients with at least one contraindication selected from:
  - renal disease, renal impairment or renal dysfunction (e.g., as specified by product information of locally approved metformin),
  - dehydration,
  - unstable or acute congestive heart failure,
  - acute or chronic metabolic acidosis, and
  - hereditary galactose intolerance;

and

- patients who suffer from one or more intolerable side effects attributed to metformin, particularly gastrointestinal side effects associated with metformin, such as for example patients suffering from at least one gastrointestinal side effect selected from:
  - nausea,
  - vomiting,
  - diarrhea,
  - intestinal gas, and
  - severe abdominal discomfort.